Check for updates

1 Department of Emergency Medicine, Oregon Health and Science University, Portland, OR, USA

2 Department of Emergency Medicine, University of California Davis, Sacramento, CA

3 Oregon Health and Science University, Portland, OR

4 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands

5 Department of Emergency Medicine, Wayne State School of Medicine, Detroit, MI

Correspondence to B Maughan
maughabr@ohsu.edu

Cite this as: *BMJ* 2024;384:e071662
http://dx.doi.org/10.1136/bmj-2022-071662
Published: 8 February 2024

EASILY MISSED?

Pulmonary embolism

Brandon C Maughan, [1] Angela F Jarman, [2] Alexa Redmond, [3] Geert-Jan Geersing, [4] Jeffrey A Kline[5]

What you need to know

- Diagnosis of pulmonary embolism (PE) is frequently missed. An estimated 12-36% of patients with PE are misdiagnosed during initial evaluation in emergency departments or primary care clinics
- Delayed and missed diagnoses are more common in older adults, in patients with chronic cardiopulmonary disease, those with low pre-test risk of PE, and in patients presenting with cough or gradual onset dyspnoea. Most patients with PE have no symptoms of deep vein thrombosis, and many have no chest pain.
- Using D-dimer thresholds adjusted for age or probability may reduce false positive results and rates of computed tomography pulmonary angiography scans.

A 71 year old woman with hypertension, coronary artery disease, and heart failure presents to her GP with fatigue and breathlessness at rest over the past 10 days. She reports a mild non-productive cough and occasional sore throat during this time, and says that deep breaths make her chest feel "heavy." She has had no fever, chest pain, abdominal pain, leg pain, or other abnormal symptoms apart from a brief episode of near syncope a few days ago that resolved without intervention. Her heart rate is 96 beats/min, blood pressure 148/78, respiratory rate 22 breaths/min, and she has an oxygen saturation level of 92% on room air; she is afebrile.

On examination, she has mild tachypnoea but no jugular venous distension, no cardiac murmur, and normal lung sounds. She has trace swelling of both lower legs and normal distal pulses. An electrocardiogram (ECG) shows sinus rhythm without evidence of ischaemia. Point-of-care tests for covid-19 and influenza are both negative. The clinician suspects the patient may have mild heart failure or a viral bronchitis and advises her to double her furosemide dose over the next three days.

The woman calls the clinic four days later with continued breathlessness. She is referred to the emergency department for further evaluation. A chest x ray is normal, and she has an elevated D-dimer concentration (1500 ng/mL). A computed tomography pulmonary angiogram (CTPA) scan subsequently identifies emboli in the bilateral main and lobar pulmonary arteries.

What is pulmonary embolism?

Pulmonary embolism (PE) is a blood clot in the pulmonary arteries, which most often results from the migration of a deep vein thrombosis (DVT) from the lower extremities through the inferior vena cava to the right heart and the pulmonary arteries. In severe cases, PE can produce a rapid increase in right ventricular afterload leading to acute right ventricular failure and obstructive shock, but PE may also present with subtle, non-specific signs and symptoms.

How common is it?

Annual age adjusted PE incidence varies by setting and roughly ranges from 39 per 100 000 adults in Hong Kong to 121 cases per 100 000 adults in the US, although differences in epidemiological reporting limit comparison.[1-4] Incidence increases substantially with age, particularly after age 70. High and upper middle income countries have 2.4-4.8 times higher incidence of venous thromboembolism (VTE) than low and lower middle income countries, even after adjustment for VTE risk factors; the cause of this association is unclear.[5] Incidence of PE has roughly doubled in both the UK and the US since the late 1990s.[6 7] Time series analysis suggests this rise is the result, primarily, of increasing use of high resolution CTPA, which has higher sensitivity than previous diagnostic tests such as lung ventilation-perfusion scintigraphy (VQ scan).[8]

Why and how often is PE diagnosis missed?

Most patients with PE are diagnosed during evaluation in the emergency department, according to predominantly retrospective literature (table 1). While definitions of missed or delayed PE diagnosis vary widely across studies, research evaluating missed diagnoses tends to assess whether patients eventually diagnosed with PE had consistent symptoms during the index visit. Literature from China, Turkey, the US, and four European countries suggests 12-36% of patients with PE in emergency departments or primary care initially receive an incorrect diagnosis.[9-15] Among patients with a "major" PE identified at autopsy (PE in a segmental or larger branch), only an estimated 12-32% had an antemortem PE diagnosis.[16]

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. To suggest a topic for this series, please email us at practice@bmj.com.

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

SHOUT
SHARE
IT

Table 1 | Evidence of missed diagnosis of pulmonary embolism

Author	Year	Country (number of centres)	N	Study design	Diagnosis category	Proportion
Kline[9]	2007	United States (1)	161	Prospective cohort of ED patients. Patients with delayed diagnosis all had PE related symptoms on arrival	Normal: diagnosed in ED	87.6%
					Delayed: 1-48 h after admission	12.4%
Smith[14]	2012	United States (1)	400	Retrospective cohort of ED patients presenting with symptoms suggestive of PE	Normal: within 12 h of arrival	81.7%
					Delayed: >12 h after ED arrival	18.3%
Torres-Macho[11]	2013	Spain (3)	436	Retrospective cohort of ED patients presenting with symptoms suggestive of PE	Normal: during initial ED visit	66.5%
					Delayed: during admission to hospital	21.6%
					Delayed: during subsequent ED visit	11.9%
Walen[32]	2016	Netherlands (1)	261	Retrospective cohort of patients referred from primary care to pulmonology clinic	Normal: < 24 h after evaluation	82.0%
					Delayed: 24-72 h after evaluation	11.9%
					Delayed: >72 h after evaluation	6.1%
Mansella[10]	2020	Switzerland (1)	226	Retrospective cohort of ED patients with any cardiac or pulmonary testing	Normal: within 24 h of arrival	81.5%
					Delayed: 1-30 days after arrival	19.5%

ED=emergency department; PE=pulmonary embolism.

PE diagnosis is often missed because presentations are highly variable and may even be asymptomatic. A 2007 systematic review identified several elements from patients' history and clinical examination associated with PE, including dyspnoea (positive likelihood ratio, PLR 1.4), recent surgery (PLR 1.6), prior VTE (PLR 1.5), syncope (PLR 2.4), and active cancer (PLR 1.7).[17] While haemoptysis is associated with PE (PLR 3.4) in patients under 50 (but not in older patients[18]), it is present in less than 10% of cases of PE, limiting its usefulness.[18 19] Although 40% of patients (range 16-51%) with PE do not have specific risk factors for PE, such as malignancy or recent orthopaedic surgery, [19 -22] physicians may perceive the risk of PE to be so low in these patients that risks of further PE evaluation (eg, false positive tests leading to unnecessary anticoagulation) could outweigh any benefit.

Since many symptoms of PE are common and can originate from a non-PE cause, they may be attributed to more common conditions. For instance, a retrospective cohort study of 436 emergency department patients in Spain found that individuals with PE who were initially misdiagnosed often presented with fever, haemoptysis, or a pulmonary infiltrate on chest x ray.[11 13] Indeed, most missed PEs are misdiagnosed as respiratory infections (43%), heart failure (27%), or exacerbations of chronic obstructive pulmonary disease (COPD) (8%), suggesting that physicians may prematurely close the differential diagnosis in patients with dyspnoea or cough,[11 23] particularly if they have a history of chronic cardiopulmonary disease such as heart failure and chronic obstructive pulmonary disease.[11] For example, in a multicentre cross sectional study of 740 French patients with a history of COPD who were admitted to hospital with worsening respiratory symptoms, combined use of a clinical probability assessment, D-dimer, and CTPA within 48 hours of admission identified PE (that had not been diagnosed at initial presentation) in 6% of patients.[24]

Diagnostic delay or misdiagnosis also appears to be more common in patients aged 65 or older,[23 25] in people with altered mental status,[9] or in those with cough as the main presenting symptom.[12] Additionally, patients with less acute PE presentations, such as gradual onset dyspnoea, may be more likely to experience an initial misdiagnosis because physicians associate PE with a sudden onset of symptoms.[23] Although two single centre Italian cohort studies concluded that gradual onset symptoms were present in only 3-6% of PE cases,[20 26] a larger multicentre cohort from 12 centres in the US found that 45% of patients with PE reported a gradual onset of symptoms.[27] In contrast, patients with chest pain,[10 12 28] syncope,[23 29] or recent surgery[29] appear less likely to experience delay or misdiagnosis of PE.[30]

It is unclear whether sex of the patient makes a difference in diagnostic delay. A prospective cohort study from Turkey and a retrospective cohort study from the Netherlands suggest that female patients may have longer delays to PE presentation and diagnosis,[12 31] whereas two retrospective cohort studies from Switzerland and the Netherlands found no such association.[10 32]

Why does early diagnosis matter?

Randomised controlled trials show that anticoagulation therapy after PE is associated with a substantially lower risk of VTE recurrence.[33 34] Observational data additionally support an association between early treatment and reduced mortality and morbidity related to PE.[9 25]

For example, a prospective cohort study of 161 patients in the US who were diagnosed with PE after hospital admission from an

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

emergency department experienced a longer median time to heparin administration (33 hours *v* 7.7 hours, P<0.001) and had more frequent adverse in-hospital outcomes, including intubation, shock, or death (30% *v* 8.5%, P=0.01) compared with patients diagnosed with PE in an emergency department before hospital admission.[9] Similarly, in a retrospective cohort study of 2250 Australian patients who presented to an emergency department with breathlessness or chest pain, diagnosis of PE in the emergency department was associated with lower in-hospital mortality (odds ratio, OR, 0.31; 95% confidence interval, CI, 0.24 to 0.47), 7 day mortality (OR 0.32; 95% CI 0.19 to 0.53), and 30 day mortality (OR 0.3; 95% CI 0.2 to 0.44) compared with inpatient diagnosis, after adjusting for age and comorbidities.[25] As observational trials, these studies do not control for variables that could confound the association between diagnostic delay and adverse outcomes and cannot prove causality.

Other trials support an association between delayed administration of heparin therapy and adverse outcomes among patients with PE. For example, a retrospective analysis assessed outcomes after delayed heparin administration in 400 symptomatic patients diagnosed with PE in the emergency department setting in the US.[35] The median time from emergency department arrival to CT diagnosis was 2.4 hours (interquartile range 1.4-7.6 hours), and heparin therapy started in the emergency department was associated with lower in-hospital mortality compared with heparin started during admission to hospital (1.4% *v* 6.7%; OR 0.2; 95% CI 0.06 to 0.69; P=0.009). In patients who survived to hospital discharge compared with those who died, the median time to achieve a therapeutic activated partial thromboplastin time (aPTT) was faster (10.7 hours (interquartile range 7.7-16.6) *v* 20.9 hours (interquartile range 8.4-28.8); P<0.001). Direct oral anticoagulants (DOACs) are associated with lower rates of haemorrhagic complications compared with unfractionated heparin, but no comparable published data are available regarding PE outcomes and timeliness of DOAC administration.

Early anticoagulation may also affect long term outcomes. In a prospective cohort study of 254 patients with PE in France, delayed PE diagnosis was associated with incomplete clot resolution on follow-up imaging at six months (OR 1.17 per 10 days; 95% CI 1.04 to 1.31).[36] Impaired clot resolution is a risk factor for chronic thromboembolic pulmonary hypertension (CTEPH), and delayed diagnosis of PE more than two weeks after symptom onset is associated with subsequent diagnosis of CTEPH (OR 7.9; 95% CI 3.3 to 19.0).[37 38]

How is PE diagnosed?

Timely, accurate diagnosis of PE depends on a clinician's initial assessment and their index of suspicion. The initial consideration of PE and decision to pursue further evaluation is considered by many the most difficult element in the diagnostic process. Correct use of decision rules can help physicians identify patients who are appropriate for D-dimer screening or who have very low probability of PE based on clinical criteria alone (eg, the pulmonary embolism rule-out criteria, or PERC, rule).[39]

The most common symptoms of PE are dyspnoea at rest and pleuritic chest pain,[19] although cluster analysis suggests the number and severity of presenting symptoms differ greatly based on age, comorbid conditions, and distribution of PE embolic burden.[40] Central emboli may cause significant dyspnoea, whereas peripheral emboli may cause little or none[4] (table 2). Dyspnoea (at rest or on exertion) has a small but significant positive likelihood ratio for PE (PLR 1.4, 95% CI 1.1 to 1.8), whereas the PLR for pleuritic chest pain is not significantly greater than 1.[17] Data on the predictive value of tachycardia for PE is mixed. A 2007 systematic review of 18 studies concluded that tachycardia was not significantly associated with PE diagnosis[17]; in contrast, a 2015 analysis of the PERC dataset concluded that tachycardia was a significant predictor of PE diagnosis in patients over age 35 (odds ratio 1.5, 95% CI 1.2 to 1.9) but not in younger adults.[45]

Table 2 | Pulmonary embolism symptoms

Signs and symptoms	Prevalence (range)
Dyspnoea	
- Any[19 20 41_44]	56-86%
- At rest[19 41]	50-61%
- On exertion[19 41]	16-27%
Chest pain	
- Any[19 20 41_44]	31-70%
- Pleuritic[19 41]	39-47%
- Non-pleuritic[19 41]	15-17%
Cough	
- No haemoptysis[19 41 43]	22-37%
- With haemoptysis[19 41]	3-8%
Deep vein thrombosis symptoms	
- Limb swelling[19 20 41_43]	7-38%
- Limb pain[19 20 41 43]	6-41%
Syncope[19 20 42_44]	5-26%
Fever[19 20]	6-10%

Patients with PE may also present with isolated dyspnoea on exertion. A 2023 prospective cross sectional study in 14 Italian emergency departments evaluated 417 patients aged under 75 without prior VTE who were referred from outpatient clinics for evaluation of new severe breathlessness on exertion with or without other cardiopulmonary signs or symptoms.[46] Among 204 patients with isolated dyspnoea on exertion (eg, no chest pain, pedal oedema, tachycardia, or haemoptysis), 114 patients (56%) underwent

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

CTPA owing to elevated D-dimer concentrations. In this group, nearly 20% (40/114) had PE diagnosed on CT imaging. However, since this sample consisted of patients specifically referred from outpatient clinics for unexplained new dyspnoea, these results may not be generalisable to general emergency department settings which typically have a far lower prevalence of patients with PE.

Appropriate testing for PE requires balancing its potential harms and benefits: high rates of testing in patient populations with low prevalence of PE can result in false positive diagnosis or diagnosis of small, clinically insignificant emboli (ie, overdiagnosis) for which anticoagulation therapy may pose more risk than benefit.[47 -51] Further, frequent CT imaging may result in patient harms including unnecessary radiation exposure from diagnostic imaging and delays in care, as well as system-level harms, costs, and adverse environmental impacts. Guidelines thus recommend strategies to exclude PE in low risk patients without imaging. For patients with symptoms concerning for PE, the approach to diagnosis typically consists of a two step process starting with estimation of PE risk using validated decision tools (eg, Wells' or revised Geneva scores, see table 3) or clinical judgment, followed by D-dimer screening in most patients.[4 52 53 56] Patients are typically classified into low, intermediate, or high risk categories with estimated PE prevalence of 7-13%, 32-43%, and 58-72%, respectively.[57] After pretest risk assessment, low and intermediate risk patients warrant screening for PE with D-dimer; retrospective studies suggest 10-50% of CTPA tests are potentially avoidable with appropriate D-dimer screening.[58 -60] Diagnostic imaging is indicated in patients with elevated D-dimer concentrations as well as in patients with high pretest probability. A 2022 individual patient level meta-analysis of 20 533 patients in 16 studies found a pooled missed PE rate ranging from 0.36% to 0.58% using this two step approach,[61] a consistent finding across different healthcare settings.[62]

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

Table 3 | Clinical decision tools for pulmonary embolism (PE) diagnostic testing

Name	Wells' criteria[52]		PE rule-out criteria[39]		Revised Geneva score[53]		YEARS[54]		4PEPS[55]	
Year	2001		2004		2006		2017		2021	
Purpose	Identify pre-test probability of PE		Identify patients in whom PE may be excluded clinically. Patients must have low probability of PE to be eligible		Identify pre-test probability of PE		Identify PE pre-test probability and D-dimer test threshold		Identify PE pre-test probability and D-dimer test threshold	
	Element	Score	Element	Score	Element	Score	Element	Score	Element	Score
Presenting signs and symptoms	Signs and symptoms of DVT	3	Unilateral leg swelling	1	Unilateral leg oedema and tenderness	4	Signs and symptoms of DVT	1	Calf pain and/or unilateral lower limb oedema	3
					Haemoptysis	1			Chest pain and acute dyspnoea	1
									Syncope	2
	Demographics				Age > 50 years	1	Age > 65 years	1	Age < 50 years	-2
			Age 50-64 years						-1	
								Male sex	2	
Clinical gestalt	PE most likely diagnosis	3					PE most likely diagnosis	1	PE most likely diagnosis	5
Surgery/immobilisation	1.5	Surgery with general anaesthesia within 4 weeks	1	Surgery or lower limb fracture within 1 month	2	Surgery, lower limb plaster cast, or bedridden >3 days within 4 weeks	2	Cancer within 6 months (active or treated)	1	
Vital signs	> 100 beats/min	1.5	> 100 beats/min	1	≥ 95 beats/min	5				
					75-94 beats/min	3				
			SpO2 < 95% on room air	1					SpO2 < 95% on room air	3
Medication			Current oestrogen use	1					Current oestrogen use	2

Name	Medical history													
Year														
Purpose														
	Element	Score	Element	Score	Element	Score	Element	Score	Element	Score	Element	Score	Element	Score
Presenting signs and symptoms	Unilateral leg pain	3	Haemoptysis	2	Haemoptysis	1								
Clinical gestalt	Medical history		Prior VTE	1.5	Prior VTE	1	Prior VTE	3			Prior VTE	2		
Surgery/immobilisation			Cancer within 12 months (active or treated)	2									Chronic respiratory disease	-1
Vital signs							< 80 beats/min	-1						

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

Table 3 | Clinical decision tools for pulmonary embolism (PE) diagnostic testing *(Continued)*

Name	Wells' criteria[52]		PE rule-out criteria[39]		Revised Geneva score[53]		YEARS[54]		4PEPS[55]					
Year	2001		2004		2006		2017		2021					
Purpose	Identify pre-test probability of PE		Identify patients in whom PE may be excluded clinically. Patients must have low probability of PE to be eligible		Identify pre-test probability of PE		Identify PE pre-test probability and D-dimer test threshold		Identify PE pre-test probability and D-dimer test threshold					
Results	Result	Total	Result	Total	Result	Total	Result	Total	Result	Total				
	Low PE probability	0-1	Very low probability, no further testing	0	Low	0-3	Use 1000 ng/mL D-dimer threshold	0	Very low probability, no further testing	<0				
	Intermediate PE probability	2-6			Intermediate	4-10			Low probability, use 1000 ng/mL D-dimer threshold	0-5				
	High probability, order imaging	≥ 13	Screen with D-dimer	≥ 1			Use 500 ng/mL D-dimer threshold	≥ 1	Moderate probability, use D-dimer threshold of 500 ng/mL or < (age × 100) ng/mL	6-12	High PE probability	≥ 7	High	≥ 11

DVT=deep vein thrombosis; VTE=venous thromboembolism.

D-dimer levels increase with age, therefore the conventional D-dimer threshold of 500 ng/mL has a diagnostic specificity of less than 25% in patients over 70.[63] As a result, in some settings, D-dimer utilisation is low despite clinical algorithms and Choosing Wisely recommendations endorsing its use to avoid unnecessary CT scans.[64-66] Several new D-dimer strategies improve test specificity and may improve use of D-dimer screening. Age adjusted D-dimer thresholds, for example, substantially improve screening efficiency with an extremely small increase (0.4-0.52%) in missed diagnoses.[4 61 67] The YEARS and 4PEPS strategies use a bayesian approach such that patients with low pre-test probability may use a higher D-dimer threshold for subsequent imaging (eg, 1000 ng/mL), notably increasing test specificity with only a small reduction in sensitivity.[54 68]

In emergency care settings, PE is often excluded without D-dimer testing in patients who are at low risk and negative for all eight clinical variables in PERC: age ≥ 50 years, heart rate ≥ 100 beats/min, oxygen saturation < 95% on room air; unilateral leg swelling; haemoptysis, surgery or trauma within four weeks; exogenous oestrogen use; or prior VTE.[39] This strategy was shown to be safe in the aforementioned large, patient level meta-analysis with a pooled failure rate of 0.9%.[62] Exclusion of PE using a low risk pre-test probability by itself (ie, without PERC) has not been validated as a safe or reliable strategy.

The most common diagnostic imaging modality for PE is CTPA, which has replaced planar ventilation-perfusion (V/Q) imaging as the gold standard in most settings because of its higher sensitivity, rapid availability, and ability to identify other acute cardiopulmonary conditions.[8] V/Q SPECT (ventilation-perfusion single photon emission CT) is a newer scintigraphic modality that captures three dimensional images and offers equal diagnostic accuracy as CTPA while delivering a lower absorbed dose of radiation.[55 69 70] V/Q SPECT testing for PE is widely available in

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

some countries (eg, Canada, France, Australia) but remains rare in others.[71]

How is it managed?

Management of PE varies widely based on haemodynamic stability and the presence of risk factors for mortality. Patients with high risk ("massive") PE present with haemodynamic instability and typically undergo systemic thrombolysis, with surgical embolectomy or catheter based intervention reserved for patients with refractory shock or contraindications to systemic thrombolysis. Definitions of intermediate risk ("sub-massive") PE differ but generally encompass haemodynamically stable patients with right ventricular dysfunction (eg, dilated right ventricle on imaging studies; elevated cardiac biomarker levels) or other risk factors, as measured by the simplified PE severity index.[4 72] Anticoagulation and admission to hospital are standard for these patients, with more intensive interventions considered based on haemodynamic status, clinical trajectory, and other patient factors. Patients with low risk PE (eg, haemodynamically stable, no right ventricular dysfunction, no mortality risk factors) were historically treated briefly in hospital, but recent guidelines suggest these patients can be considered for outpatient management where feasible, as this strategy has been shown to be safe and may be associated with fewer adverse events than with admission.[4 72 73]

Reflections on the case study

The patient in this case reported new dyspnoea at rest, which is the single most common symptom of PE. Symptoms from missed PEs are often attributed to chronic disease (eg, heart failure) or new respiratory infection for which confirmatory testing may not be available. The patient had no rales, weight change, or significant leg oedema to suggest a heart failure exacerbation. The critical step in this case was for the treating physician to consider PE as a diagnosis: even though the patient's risk of PE was not high, there was no strong evidence on history or examination to clearly indicate an alternative diagnosis. Decision tools for PE would classify the patient's risk as low (Wells' or 4PEPS) or moderate (revised Geneva), and PERC is not applicable based on the patient's age. Together, these suggest the need for D-dimer testing. D-dimer screening during the initial visit would have prompted earlier imaging and an earlier diagnosis. PE incidence increases substantially with age, and many patients with PE—especially older patients—may not have classic symptoms such as pleuritic chest pain or leg swelling and pain.

Education into practice

- Which elements in a patient's history (eg, signs, symptoms, or risk factors) are more or less likely to prompt you to consider PE? If isolated chest pain (without dyspnoea) would prompt you to evaluate a patient for PE, would you do the same for isolated dyspnoea?
- How does the sudden onset or recency of symptoms influence your decision to test for PE?

How patients were involved in creation of the article

The authors engaged in discussions with patients in the emergency department with current or prior diagnosis of PE. Anecdotally, respondents' comments mirrored study results mentioned in this article, including expedited evaluation for post-surgical symptoms and delayed evaluation for isolated dyspnoea. Several respondents expressed uncertainty about seeking care for mild symptoms. Two respondents described frustration with misdiagnosis of "musculoskeletal chest pain" in the absence of preceding injury or other compelling history to suggest musculoskeletal cause of pain.

How this article was made

The authors performed an initial search on OVID Medline on 1 April 2022 for English language articles published between 2000 and 2022 with key terms "pulmonary embolism" and any of "delayed diagnosis", "diagnostic delay", or "missed diagnosis". The search was repeated on 1 October 2022 to identify interim publications. Case reports and letters to the editor were excluded. We also reviewed guidelines on PE diagnosis and management from US and European medical societies. We reviewed all relevant articles and performed manual review of reference lists for included publications.

Competing interests: *The BMJ* has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: none.

Further details of *The BMJ* policy on financial interests are here: https://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests

Provenance and peer review: commissioned; externally peer reviewed.

1 Centers for Disease Control and Prevention (CDC). Venous thromboembolism in adult hospitalizations—United States, 2007-2009. *MMWR Morb Mortal Wkly Rep* 2012;61:-4.pmid: 22672974
2 Cheuk BLY, Cheung GCY, Cheng SWK. Epidemiology of venous thromboembolism in a Chinese population. *Br J Surg* 2004;91:-8. doi: 10.1002/bjs.4454 pmid: 15048741
3 Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. *Circ Res* 2016;118:-7. doi: 10.1161/CIRCRESAHA.115.306841 pmid: 27126645
4 Konstantinides SV, Meyer G, Becattini C, etalESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J* 2020;41:-603. doi: 10.1093/eurheartj/ehz405 pmid: 31504429
5 Siegal DM, Eikelboom JW, Lee SF, etalVenous Thromboembolism Collaboration. Variations in incidence of venous thromboembolism in low-, middle-, and high-income countries. *Cardiovasc Res* 2021;117:-84. doi: 10.1093/cvr/cvaa044 pmid: 32142099
6 Kempny A, McCabe C, Dimopoulos K, etal. Incidence, mortality and bleeding rates associated with pulmonary embolism in England between 1997 and 2015. *Int J Cardiol* 2019;277:-34. doi: 10.1016/j.ijcard.2018.10.001 pmid: 30448018
7 Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med* 2011;171:-7. doi: 10.1001/archinternmed.2011.178 pmid: 21555660
8 Wang RC, Miglioretti DL, Marlow EC, etal. Trends in imaging for suspected pulmonary embolism across US health care systems, 2004 to 2016. *JAMA Netw Open* 2020;3:e2026930. doi: 10.1001/jamanetworkopen.2020.26930 pmid: 33216141
9 Kline JA, Hernandez-Nino J, Jones AE, Rose GA, Norton HJ, Camargo CAJr. Prospective study of the clinical features and outcomes of emergency department patients with delayed diagnosis of pulmonary embolism. *Acad Emerg Med* 2007;14:-8. doi: 10.1197/j.aem.2007.03.1356 pmid: 17554011
10 Mansella G, Keil C, Nickel CH, etal. Delayed diagnosis in pulmonary embolism: frequency, patient characteristics, and outcome. *Respiration* 2020;99:-97. doi: 10.1159/000508396 pmid: 32694258
11 Torres-Macho J, Mancebo-Plaza AB, Crespo-Giménez A, etal. Clinical features of patients inappropriately undiagnosed of pulmonary embolism. *Am J Emerg Med* 2013;31:-50. doi: 10.1016/j.ajem.2013.08.037 pmid: 24060320
12 Hendriksen JMT, Koster-van Ree M, Morgenstern MJ, etal. Clinical characteristics associated with diagnostic delay of pulmonary embolism in primary care: a retrospective observational study. *BMJ Open* 2017;7:e012789. doi: 10.1136/bmjopen-2016-012789 pmid: 28279993
13 Ray P, Birolleau S, Lefort Y, etal. Acute respiratory failure in the elderly: etiology, emergency diagnosis and prognosis. *Crit Care* 2006;10:. doi: 10.1186/cc4926 pmid: 16723034
14 Smith SB, Geske JB, Morgenthaler TI. Risk factors associated with delayed diagnosis of acute pulmonary embolism. *J Emerg Med* 2012;42:-6. doi: 10.1016/j.jemermed.2011.06.004 pmid: 21958453
15 Kwok CS, Wong CW, Lovatt S, Myint PK, Loke YK. Misdiagnosis of pulmonary embolism and missed pulmonary embolism: A systematic review of the literature. *Health Sci Rev (Oxf)* 2022;3:100022doi: 10.1016/j.hsr.2022.100022.
16 Micallef MJ. The autopsy and diagnosis of pulmonary thrombo-embolism. *Forensic Sci Med Pathol* 2018;14:-3. doi: 10.1007/s12024-018-9950-5 pmid: 29399729
17 West J, Goodacre S, Sampson F. The value of clinical features in the diagnosis of acute pulmonary embolism: systematic review and meta-analysis. *QJM* 2007;100:-9. doi: 10.1093/qjmed/hcm113 pmid: 18089542
18 Le Gal G, Righini M, Roy PM, etal. Differential value of risk factors and clinical signs for diagnosing pulmonary embolism according to age. *J Thromb Haemost* 2005;3:-64. doi: 10.1111/j.1538-7836.2005.01598.x pmid: 16241944
19 Pollack CV, Schreiber D, Goldhaber SZ, etal. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). *J Am Coll Cardiol* 2011;57:-6. doi: 10.1016/j.jacc.2010.05.071 pmid: 21292129

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

20 Miniati M, Cenci C, Monti S, Poli D. Clinical presentation of acute pulmonary embolism: survey of 800 cases. *PLoS One* 2012;7:e30891. doi: 10.1371/journal.pone.0030891 pmid: 22383978

21 Stoeva N, Kirova G, Staneva M, Lekova D, Penev A, Bakalova R. Recognition of unprovoked (idiopathic) pulmonary embolism-Prospective observational study. *Respir Med* 2018;135:-61. doi: 10.1016/j.rmed.2018.01.001 pmid: 29414454

22 White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107(Suppl 1):-8. doi: 10.1161/01.CIR.0000078468.11849.66 pmid: 12814979

23 Alonso-Martínez JL, Sánchez FJ, Echezarreta MA. Delay and misdiagnosis in sub-massive and non-massive acute pulmonary embolism. *Eur J Intern Med* 2010;21:-82. doi: 10.1016/j.ejim.2010.04.005 pmid: 20603035

24 Couturaud F, Bertoletti L, Pastre J, etalPEP Investigators. Prevalence of pulmonary embolism among patients with COPD hospitalized with acutely worsening respiratory symptoms. *JAMA* 2021;325:-68. doi: 10.1001/jama.2020.23567 pmid: 33399840

25 Jelinek GA, Ingarfield SL, Mountain D, Gibson NP, Jacobs IG. Emergency Department diagnosis of pulmonary embolism is associated with significantly reduced mortality: a linked data population study. *Emerg Med Australas* 2009;21:-76. doi: 10.1111/j.1742-6723.2009.01196.x pmid: 19682011

26 Miniati M, Prediletto R, Formichi B, etal. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. *Am J Respir Crit Care Med* 1999;159:-71. doi: 10.1164/ajrccm.159.3.9806130 pmid: 10051264

27 Courtney DM, Kline JA, Kabrhel C, etal. Clinical features from the history and physical examination that predict the presence or absence of pulmonary embolism in symptomatic emergency department patients: results of a prospective, multicenter study. *Ann Emerg Med* 2010;55:-315.e1. doi: 10.1016/j.annemergmed.2009.11.010 pmid: 20045580

28 Jenab Y, Alemzadeh-Ansari MJ, Fehri SA, Ghaffari-Marandi N, Jalali A. Effect of delay in hospital presentation on clinical and imaging findings in acute pulmonary thromboembolism. *J Emerg Med* 2014;46:-71. doi: 10.1016/j.jemermed.2013.09.014 pmid: 24462027

29 Ozsu S, Oztuna F, Bulbul Y, etal. The role of risk factors in delayed diagnosis of pulmonary embolism. *Am J Emerg Med* 2011;29:-32. doi: 10.1016/j.ajem.2009.07.005 pmid: 20825770

30 van Maanen R, Trinks-Roerdink EM, Rutten FH, Geersing GJ. A systematic review and meta-analysis of diagnostic delay in pulmonary embolism. *Eur J Gen Pract* 2022;28:-72. doi: 10.1080/13814788.2022.2086232 pmid: 35730378

31 Aydogdu M, Dogan NO, Sinanoğlu NT, etal. Delay in diagnosis of pulmonary thromboembolism in emergency department: is it still a problem?*Clin Appl Thromb Hemost* 2013;19:-9. doi: 10.1177/1076029612440164 pmid: 22496086

32 Walen S, Damoiseaux RA, Uil SM, van den Berg JW. Diagnostic delay of pulmonary embolism in primary and secondary care: a retrospective cohort study. *Br J Gen Pract* 2016;66:-50. doi: 10.3399/bjgp16X685201 pmid: 27114207

33 Chopard R, Albertsen IE, Ecarnot F, etal. Extended anticoagulation after pulmonary embolism: a multicenter observational cohort analysis. *J Am Heart Assoc* 2022;11:e024425. doi: 10.1161/JAHA.121.024425 pmid: 35730608

34 Khan F, Rahman A, Carrier M, etalMARVELOUS Collaborators. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. *BMJ* 2019;366:. doi: 10.1136/bmj.l4363 pmid: 31340984

35 Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early anticoagulation is associated with reduced mortality for acute pulmonary embolism. *Chest* 2010;137:-90.

36 Sanchez O, Helley D, Couchon S, etal. Perfusion defects after pulmonary embolism: risk factors and clinical significance. *J Thromb Haemost* 2010;8:-55.

37 Fernandes T, Auger W, Fedullo P. Epidemiology and risk factors for chronic thromboembolic pulmonary hypertension. *Thromb Res* 2018;164:-9.

38 Klok FA, Dzikowska-Diduch O, Kostrubiec M, etal. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. *J Thromb Haemost* 2016;14:-8.

39 Kline JA, Courtney DM, Kabrhel C, etal. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. *J Thromb Haemost* 2008;6:-80. doi: 10.1111/j.1538-7836.2008.02944.x pmid: 18318689

40 Ji Q-Y, Wang M-F, Su C-M, etal. Clinical symptoms and related risk factors in pulmonary embolism patients and cluster analysis based on these symptoms. *Sci Rep* 2017;7:. doi: 10.1038/s41598-017-14888-7 pmid: 29097743

41 Stein PD, Beemath A, Matta F, etal. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. *Am J Med* 2007;120:-9.

42 Pribish AM, Beyer SE, Krawisz AK, Weinberg I, Carroll BJ, Secemsky EA. Sex differences in presentation, management, and outcomes among patients hospitalized with acute pulmonary embolism. *Vasc Med* 2020;25:-8.

43 Robert-Ebadi H, Le Gal G, Carrier M, etal. Differences in clinical presentation of pulmonary embolism in women and men. *J Thromb Haemost* 2010;8:-8.

44 Keller K, Rappold L, Gerhold-Ay A, etal. Sex-specific differences in pulmonary embolism. *Thromb Res* 2019;178:-81.

45 Mongan J, Kline J, Smith-Bindman R. Age and sex-dependent trends in pulmonary embolism testing and derivation of a clinical decision rule for young patients. *Emerg Med J* 2015;32:-5.

46 Prandoni P, Lensing AWA, Prins MH, etalPulmonary Embolism Dyspnea Italian Study (PEDIS) Investigators. Prevalence of pulmonary embolism among patients with recent onset of dyspnea on exertion. A cross-sectional study. *J Thromb Haemost* 2023;21:-75. doi: 10.1016/j.jtha.2022.09.007 pmid: 36695397

47 Costantino G, Norsa AH, Amadori R, etal. Interobserver agreement in the interpretation of computed tomography in acute pulmonary embolism. *Am J Emerg Med* 2009;27:-11.

48 Courtney DM, Miller C, Smithline H, Klekowski N, Hogg M, Kline JA. Prospective multicenter assessment of interobserver agreement for radiologist interpretation of multidetector computerized tomographic angiography for pulmonary embolism. *J Thromb Haemost* 2010;8:-9.

49 Hutchinson BD, Navin P, Marom EM, Truong MT, Bruzzi JF. Overdiagnosis of pulmonary embolism by pulmonary CT angiography. *AJR Am J Roentgenol* 2015;205:-7.

50 Miller WT, Marinari LA, Barbosa E, etal. Small pulmonary artery defects are not reliable indicators of pulmonary embolism. *Ann Am Thorac Soc* 2015;12:-9.

51 Pena E, Kimpton M, Dennie C, Peterson R, Le Gal G, Carrier M. Difference in interpretation of computed tomography pulmonary angiography diagnosis of subsegmental thrombosis in patients with suspected pulmonary embolism. *J Thromb Haemost* 2012;10:-8.

52 Wells PS, Anderson DR, Rodger M, etal. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and d-dimer. *Ann Intern Med* 2001;135:.

53 Le Gal G, Righini M, Roy PM, etal. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. *Ann Intern Med* 2006;144:-71.

54 Van Der Hulle T, Cheung WY, Kooij S, etal. Simplified diagnostic management of suspected pulmonary embolism (the YEARS study): a prospective, multicentre, cohort study. *Lancet* 2017;390:-97.

55 Isidoro J, Gil P, Costa G, Pedroso de Lima J, Alves C, Ferreira NC. Radiation dose comparison between V/P-SPECT and CT-angiography in the diagnosis of pulmonary embolism. *Phys Med* 2017;41:-6. doi: 10.1016/j.ejmp.2017.04.026 pmid: 28487206

56 Raja AS, Greenberg JO, Qaseem A, etal. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the clinical guidelines Committee of the American College of Physicians. *Ann Intern Med* 2015;163:-11.

57 Penaloza A, Verschuren F, Meyer G, etal. Comparison of the unstructured clinician gestalt, the Wells score, and the revised Geneva score to estimate pretest probability for suspected pulmonary embolism. *Ann Emerg Med* 2013;62:.

58 Dhakal P, Iftikhar MH, Wang L, etal. Overutilisation of imaging studies for diagnosis of pulmonary embolism: are we following the guidelines?*Postgrad Med J* 2019;95:-4. doi: 10.1136/postgradmedj-2018-135995 pmid: 30665902

59 Perelas A, Dimou A, Saenz A, etal. CT pulmonary angiography utilization in the emergency department: diagnostic yield and adherence to current guidelines. *Am J Med Qual* 2015;30:-7. doi: 10.1177/1062860614543302 pmid: 25037560

60 Soo Hoo GW, Tsai E, Vazirani S, Li Z, Barack BM, Wu CC. Long-term experience with a mandatory clinical decision rule and mandatory d-dimer in the evaluation of suspected pulmonary embolism. *J Am Coll Radiol* 2018;15:-80. doi: 10.1016/j.jacr.2018.04.031 pmid: 29907418

61 Stals MAM, Takada T, Kraaijpoel N, etal. Safety and efficiency of diagnostic strategies for ruling out pulmonary embolism in clinically relevant patient subgroups. *Ann Intern Med* 2022;175:-55. doi: 10.7326/M21-2625 pmid: 34904857

62 Geersing G-J, Takada T, Klok FA, etal. Ruling out pulmonary embolism across different healthcare settings: A systematic review and individual patient data meta-analysis. *PLoS Med* 2022;19:e1003905. doi: 10.1371/journal.pmed.1003905 pmid: 35077453

63 Schouten HJ, Geersing GJ, Koek HL, etal. Diagnostic accuracy of conventional or age adjusted D-dimer cut-off values in older patients with suspected venous thromboembolism: systematic review and meta-analysis. *BMJ* 2013;346:.

64 Kline JA, Garrett JS, Sarmiento EJ, Strachan CC, Courtney DM. Over-testing for suspected pulmonary embolism in American emergency departments. *Circ Cardiovasc Qual Outcomes* 2020;13:e005753. doi: 10.1161/CIRCOUTCOMES.119.005753 pmid: 31957477

65 Salehi L, Phalpher P, Yu H, etal. Utilization of serum D-dimer assays prior to computed tomography pulmonary angiography scans in the diagnosis of pulmonary embolism among emergency department physicians: a retrospective observational study. *BMC Emerg Med* 2021;21:. doi: 10.1186/s12873-021-00401-x pmid: 33468044

66 Sane M. Utilization of D-dimer assay, CT angiography, and the incidence of pulmonary embolism in the hospital district of Helsinki and Uusimaa (2011-2017). *J Thromb Thrombolysis* 2022;54:-82. doi: 10.1007/s11239-022-02698-2 pmid: 36116083

67 Schols AMR, Meijs E, Dinant G-J, Stoffers HEJH, Krekels MME, Cals JWL. General practitioner use of D-dimer in suspected venous thromboembolism: historical cohort study in one geographical region in the Netherlands. *BMJ Open* 2019;9:e026846. doi: 10.1136/bmjopen-2018-026846 pmid: 31142527

68 Roy P-M, Friou E, Germeau B, etal. Derivation and validation of a 4-level clinical pretest probability score for suspected pulmonary embolism to safely decrease imaging testing. *JAMA Cardiol* 2021;6:-77. doi: 10.1001/jamacardio.2021.0064 pmid: 33656522

69 Roach PJ, Schembri GP, Bailey DL. V/Q scanning using SPECT and SPECT/CT. *J Nucl Med* 2013;54:-96. doi: 10.2967/jnumed.113.124602 pmid: 23907760

70 Bhatia KD, Ambati C, Dhaliwal R, etal. SPECT-CT/VQ versus CTPA for diagnosing pulmonary embolus and other lung pathology: Pre-existing lung disease should not be a contraindication. *J Med Imaging Radiat Oncol* 2016;60:-7. doi: 10.1111/1754-9485.12471 pmid: 27461384

71 Le Roux P-Y, Pelletier-Galarneau M, De Laroche R, etal. Pulmonary scintigraphy for the diagnosis of acute pulmonary embolism: a survey of current practices in Australia, Canada, and France. *J Nucl Med* 2015;56:-7. doi: 10.2967/jnumed.115.157743 pmid: 26135110

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.

72 Stevens SM, Woller SC, Kreuziger LB, etal. Antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel Report. *Chest* 2021;160:-608. doi: 10.1016/j.chest.2021.07.055 pmid: 34352278

73 Roy PM, Corsi DJ, Carrier M, etal. Net clinical benefit of hospitalization versus outpatient management of patients with acute pulmonary embolism. *J Thromb Haemost* 2017;15:-94. doi: 10.1111/jth.13629 pmid: 28106343

BMJ: first published as 10.1136/bmj-2022-071662 on 8 February 2024. Downloaded from http://www.bmj.com/ on 10 February 2024 at Univ Of West Ontario GSTR101749364 Serials Acquisitions Unit. Protected by copyright.